Diagnosis and Staging of Gynecological Malignancies

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ABSTRACT

Accurate diagnosis and adequate staging are the foundations for successful treatment of any malignancy. The following chapter will give a short overview of symptoms and diagnostic findings in gynecological malignancies. Gynecological cancers are usually staged following the Fédération Internationale de Gynécologie et d'Obstétrique system.[1] Tumor registries often follow the TNM system to describe tumor size (T), nodal spread (N), and distant metastases (M) as recommended by the American Joint Committee on Cancer.[2] This system is identical to the classification recommended by the Union Internationale Centre le Cancer. In this review, both systems will be explained. The p TNM system describes the pathological (p) findings.

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VULVAR CANCER

Symptoms

The initial symptoms of vulvar cancer can be quite subtle. In situ disease does not cause any symptoms at all in about 50% of the cases.[3] Some patients complain of vulvar irritation and itching. Invasive lesions initially are characterized by small areas of tissue excoriation and ulceration; itching, irritation, burning on urination, and later pain are the main symptoms. As the tumor grows, this ulceration can get larger and deeper, or an exophytic tumor mass may develop involving neighboring organs. One sign of advanced disease is inguinal adenopathy, initially mobile, then fixated.[4] The diagnosis of vulvar cancer is often delayed: it develops mainly in older women who often decline gynecological screening and who, even when symptomatic, try to avoid a pelvic exam. Therefore, the patient treats the sore areas on the vulva with creams for a long time until she is so uncomfortable that she is forced to undergo an exam and the diagnosis is made. Invasive vulvar cancer may occasionally develop in young women and any lesion that does not respond to treatment should be subjected to biopsy.[5]

Diagnosis

Biopsy provides a definitive diagnosis of vulvar cancer. Because in early lesions, distinguishing the depth of invasion is critical, a tangential biopsy should be avoided at all costs. The optimal biopsy is taken with a Key's punch instrument, which assures a perpendicular specimen.[6] Squamous cell carcinoma is the most frequent histologic diagnosis, followed by melanoma, Paget's disease, adenocarcinoma, basal cell carcinoma, and Bartholin's gland carcinoma.[7] During the physical exam, the entire lower genital tract should be carefully inspected and palpated. Involvement of the urethra, vagina, and rectum should be evaluated. A complete physical examination with lymph node survey is necessary, with particular attention paid to the inguinal area. Clinical assessment of the inguinal nodes is quite inaccurate, so vulvar cancer is now staged surgically. The patient must be evaluated for metastatic disease, have a chest x-ray taken, and with larger lesions, undergo a computed tomography (CT) scan of the abdomen and pelvis to detect for pelvic adenopathy.[4]

Staging

The staging is assigned after evaluation of the histological specimen, as seen in Table I.[1,2] The following parameters are taken into consideration: tumor size, the depth of invasion (nodal metastasis is not seen if less than 1 mm), involvement of neighboring organs (vagina, urethra, bladder, and rectum), and nodal status, which is the most important prognostic factor.[8] The primary nodal group is the inguinal nodes and an adequate lymph adenectomy should contain at least 6 nodes.[9] This staging system is used for all histological types of vulvar cancer except melanoma, in which prognosis is better determined by the Breslow or Clark microscopic staging systems.[10]

EDUCATIONAL OBJECTIVE

Review the most frequently used gynecologic malignancy staging systems.

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

Staging systems for gynecologic malignancies can assist in designing proper treatment regimens before cancers advance to untreatable stages.

An understanding of the diagnostic work-up for gynecologic cancer patients with various stages of disease can assist the treatment process.

Accurate diagnosis and staging will allow for the most cost-effective treatment of gynecologic cancer patients.

Familiarity with the symptoms and staging systems for the various gynecologic malignancies can enhance the care of these patients.

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VAGINAL CANCER

Vaginal cancer is quite rare and in advanced stages, impossible to distinguish from cervical or vulvar cancers. The symptomatology, work-up, and staging system are very similar to those of cervical cancer. Again, biopsy provides a definitive diagnosis and most often reveals squamous cell carcinoma. Rarely it will reveal adenocarcinoma, melanoma, or sarcoma.[11]

CERVICAL CANCER

Symptoms

Pre-invasive cervical malignancy is always asymptomatic. Once invasion occurs and a portion of the cervical surface is destroyed by cancer, symptoms develop. Irregular vaginal spotting and bleeding are the most frequent initial signs. Postcoital spotting may be seen, but it is rarely reported. If the tumor volume is large, bleeding can lead to anemia. Foul smelling vaginal discharge is another frequent symptom of advanced cervical cancer. After further growth, the tumor

TABLE 1. FIGO AND TNM STAGING OF VULVAR CANCER

FIGO	TNM
Stage 0 Carcinoma in situ; intraepithelial carcinoma	Tis N0 M0
Stage I Tumor confined to the vulva or perineum; 2 cm or less in greatest dimension; no nodal metastasis Stage IA: stromal invasion <1.0 mm Stage IB: stromal invasion >1.0 mm	T1 N0 M0
Stage II Tumor confined to the vulva or perineum; more than 2 cm in greatest dimension; no nodal metastasis	T2 N0 M0
Stage III Tumor of any size with spread to the urethra, vagina, or anus, or with unilateral regional lymph node metastasis	T3 N0 M0 T1–3 N1 M0
Stage IVA Tumor in upper urethra, bladder mucosa, rectal mucosa, pelvic bone, or bilateral regional node metastases	T4 N any M0 T1–3 N2 M0
Stage IVB Any distant metastasis, including pelvic lymph nodes	T any N any M1

FIGO=Fédération Internationale de Gynécologie et d'Obstétrique.

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TABLE 2. STAGING OF CERVICAL CANCER

FIGO			TNM
Stage		**Definition**	
0		Carcinoma in situ; intraepithelial carcinoma	Tis N0 M0
I		Carcinoma strictly confined to the cervix (extension to the corpus is disregarded)	T1
	Ia	Invasive cancer identified only microscopically; all gross lesions even with superficial invasion are stage Ib; invasion limited to measured stromal invasion with a maximum depth of 5.0 mm and a maximum width of 7.0 mm	T1a
	Ia1	Stromal invasion <3.0 mm deep, <7.0 mm wide	T1a1 N0 M0
	Ia2	Stromal invasion 3.0–5.0 mm deep, <7.0 mm wide	T1a2 N0 M0
	Ib	Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia	T1b
	Ib1	Clinical lesions <4 cm	T1b1 N0 M0
	Ib2	Clinical lesions >4 cm	T1b2 N0 M0
II		Carcinoma extends beyond the cervix but has not extended onto the pelvic wall; carcinoma involves the vagina but not as far as the lower third	T2
	IIa	No obvious parametrial involvement	T2a N0 M0
	IIb	Obvious parametrial involvement	T2b N0 M0
III		The carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumor and the pelvic wall; the tumor involves the lower third of the vagina; all cases with a hydroureter or nonfunctioning kidney should be included unless they are due to other causes	T3
	IIIa	No extension onto the pelvic wall but involvement of the lower third of the vagina	T3a N0 M0
	IIIb	Extension to the pelvic wall or hydronephrosis or nonfunctioning kidney	T1–3a N1 M0 T3b N any M0
IV		Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum	T4
	IVa	Spread to adjacent organs	T4a N any Mo
	IVb	Spread to distant organs	T any N any M1

The FIGO staging is clinical only. Surgical findings can be described following the p TNM system. FIGO=Fédération Internationale de Gynécologie et d'Obstétrique.

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"The most important staging exam is a thorough bimanual and rectovaginal pelvic exam to evaluate tumor diameter, parametrial involvement, and fixation to the pelvic wall."

involves the neighboring organs, causing related symptoms, such as pain in the lower back, and in the case of pelvic wall involvement, pain radiating along the obturator nerve to the leg. Another later sign is leg swelling due to venous compression from enlarged lymph nodes or deep venous thrombosis related to compression and inflammatory reaction around the iliac veins. Signs of bowel or bladder involvement, or metastatic disease at time of initial presentation are very rarely seen in countries with screening programs.[12]

Diagnosis

The diagnosis is made from a tissue biopsy. Although a Pap smear is a screening test, it is inadequate for diagnostic purposes. The overall false negative rate of the Pap smear is at least 20%.[13] Therefore, a suspicious lesion on the cervix must always undergo biopsy even if the Pap smear is normal. Squamous carcinoma is the most frequent type, followed by adenocarcinoma, adeno-squamous carcinoma, and glassy cell carcinoma. Rarely seen are small cell carcinoma, lymphoma, and sarcoma.[14]

Because many patients with cervical or vaginal cancer never undergo surgery, these gynecological malignancies are the only ones which are staged clinically.[1] The most important staging exam is a thorough bimanual and rectovaginal pelvic exam to evaluate tumor diameter, parametrial involvement, and fixation to the pelvic wall. For the patient's comfort, she may be put under anesthesia while the examination is performed. Although cervical cancer initially spreads laterally towards the parametria and the pelvic wall, in advanced cases, involvement of the bladder and rectum must be ruled out by cystoscopy and proctoscopy. Other areas of possible tumor spread are the vagina, the inguinal area, and the supraclavicular area. Pulmonary and abdominal exams are usually negative at time of initial diagnosis.

A very important prognostic factor is the presence of hydronephrosis, a sign of significant parametrial or pelvic wall involvement. All patients with suspected cervical cancer should be evaluated for hydronephrosis.[15] Traditionally, this is done with an intravenous pyelogram; however, in very early lesions considered for surgical therapy, an ultrasound exam may be sufficient. All patients with larger lesions should undergo a CT scan of the abdomen and pelvis to be evaluated for adenopathy of the pelvic and para-aortic lymph nodes.[16] When compared to surgical staging, the sensitivity of a CT scan for the assessment of para-aortic nodes is about 34%, and the specificity is 96%;[17] the similar sensitivity of magnetic resonance imaging (MRI) is 55%,[18] and its specificity is 71%; and the similar sensitivity of a lymphangiogram is 79%, and its specificity is 73%.[17] Although surgical staging with pelvic and para-aortic retroperitoneal lymph node biopsy and debulking of enlarged lymph nodes is beneficial in well-selected cases,[19] there is no definite evidence that surgical staging improves overall survival.[20] A chest x-ray should always be done to rule out pulmonary metastasis; in the rare situation that a patient has suspicious symptoms, a bone scan may become necessary.

Staging

The staging of cervical cancer is clinical, and the only tests which are available worldwide are a pelvic exam, an intravenous pyelogram, cystoscopy, proctoscopy, a chest x-ray, and a bone scan. Although a CT scan of the abdomen and pelvis is performed on most patients, it cannot be used for staging purposes. In addition, findings obtained at the time of surgery, such as nodal metastasis or peritoneal disease, cannot be used for Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging, although these findings will obviously affect the choice of treatment. The staging system is summarized in Table II.[1,2] Stage I disease is confined to the cervix. Here, a distinction is made regarding depth of invasion: invasion less than 3 mm usually carries no risk of nodal metastasis; invasion between 3 mm and 5 mm carries an incidence of pelvic nodal metastasis of about 5%; and invasion greater than 5 mm carries a higher incidence of nodal metastasis. Any lesion larger than this, with deeper invasion, or which is macroscopically apparent is regarded as a IB tumor. Even large tumors can remain confined to the cervix. In such cases, overall tumor volume is of great prognostic importance. Stage IB tumors therefore are separated into two substages: tumors up to 4 cm in diameter are in stage IB1, and tumors more than 4 cm in diameter are in stage IB2. Stage IIA disease involves the upper vagina and stage IIB disease involves the parametria with no fixation to the pelvic wall. Stage IIIA disease involves the lower vagina. As the lower vaginal epithelium develops from tissue originating from

the urogenital sinus, this area drains into the inguinal lymph nodes, and in the case of tumor involvement, the inguinal lymph nodes also have to be treated. Stage IIIB disease involves fixation of the tumor to the pelvic wall on one or both sides. It also includes all patients with hydronephrosis. Stage IVA disease involves disease found within the bladder and rectum and stage IVB disease involves distant metastasis, mainly to the lungs and bones.

ENDOMETRIAL CANCER

Symptoms

Most endometrial cancers cause early symptoms such as postmenopausal bleeding, or irregular vaginal bleeding or spotting in the premenopausal or perimenopausal patient.[21] These symptoms allow patients with endometrial cancer to be diagnosed early. The risk of this disease increases with age.[22] Although it is very rare in patients under 40,[23] patients with prolonged anovulation or oligomenorrhea, specifically those with polycystic ovarian disease, are at increased risk. For these women, an endometrial biopsy is warranted whenever irregular bleeding develops. The Pap smear is highly unreliable for diagnosing endometrial cancer; it is negative in about 60% of the cases.[24] Signs of locally advanced disease, such as pelvic pain or abdominal pain, are rarely the presenting symptoms. However, papillary serous adenocarcinoma of the endometrium, which has growth characteristics similar to ovarian cancer, may present with signs of abdominal dissemination, such as ascites, without vaginal bleeding.[25]

Diagnosis

The most important diagnostic procedure is the endometrial biopsy. This test is accurate in over 95% of the cases.[26] The endometrioid adenocarcinoma is seen most frequently, sometimes with squamous metaplasia or as an adenosquamous carcinoma. Rare and more aggressive cell types are clear cell and papillary serous tumors.[27] In addition to the biopsy, an endocervical sample is indicated to rule out a primary lesion in this area. With a transvaginal ultrasound exam, the uterine cavity can be evaluated and the endometrial thickness measured. The average thickness of an endometrial cancer is about 18 mm; normal atrophic endometrium is 5 mm or less.[28] While ultrasonography cannot replace the tissue diagnosis, it can provide valuable information when the endometrial biopsy results are inconclusive. If signs of atrophy are present on a sparse biopsy and are confirmed on ultrasound, the patient may be observed.[29] Otherwise a hysteroscopy with dilatation and curettage is recommended. Hysteroscopy is particularly effective in diagnosing localized problems such as polyps.[30] During a pelvic exam, the uterus often feels normal, even if there is considerable intrauterine tumor volume. In cases of advanced disease, cervical extension may be seen or a pelvic mass may be felt. A general

"...an endometrial biopsy is warranted whenever irregular bleeding develops."

TABLE 3. STAGING OF ENDOMETRIAL CANCER

FIGO		TNM
Stage I		T1
Stage Ia	Tumor limited to endometrium	T1a N0 M0
Stage Ib	Invasion to less than one-half the myometrium	T1b N0 M0
Stage Ic	Invasion to or beyond one-half the myometrium	T1c N0 M0
Stage II		T2
Stage IIa	Endocervical glandular involvement only	T2a N0 M0
Stage IIb	Cervical stromal invasion	T2b N0 M0
Stage III		T3
Stage IIIa	Tumor invades serosa, adnexa, or both; positive peritoneal cytology	T3a N0 M0
Stage IIIb	Vaginal metastases	T3b N0 M0
Stage IIIc	Metastases to pelvic or para-aortic lymph nodes or both	T1-3b N1 M0
Stage IV		T4
Stage IVa	Tumor invasion of bladder or bowel mucosa or both	T4 N any M0
Stage IVb	Distant metastases including intra-abdominal or inguinal lymph nodes or both	T any N any M1

FIGO=Fédération Internationale de Gynécologie et d'Obstétrique.

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physical exam rarely reveals signs of metastatic disease to nodes, abdomen, or lungs. Because most patients with endo-metrial cancer will undergo surgery, a preoperative radiological work-up is less important; however, a chest x-ray should be taken in all cases.[31] In patients with serious medical complications, when limited surgery is considered or surgery is not possible at all, further information regarding the intrauterine tumor volume and depth of invasion can be gained by ultrasound or MRI. The MRI adds valuable data for evaluating nodal disease.[32] The CA-125 level is elevated in 85% of patients with extrauterine endometrial cancer.[33]

"With deep invasion into the myometrium, the risk of pelvic nodal metastasis increases significantly to 11% in grade 1 tumors, and to 34% in grade 3 tumors otherwise confined to the uterus."

Staging

Because most patients with endometrial cancer undergo surgery, the staging also is surgical. The two main parameters are invasion of the uterine wall or cervix and extrauterine disease. Careful inspection and palpation of the entire peritoneal cavity and retroperitoneal spaces are integral parts of the staging procedure, as are peritoneal washings. After the hysterectomy, the uterus is evaluated for tumor volume and depth of invasion. With deep invasion into the myometrium, the risk of pelvic nodal metastasis increases significantly to 11% in grade 1 tumors and to 34% in grade 3 tumors otherwise confined to the uterus.[34] For complete staging, evaluation of the nodal chains in the pelvic and para-aortic area is recommended, especially for all grade 3, papillary serous, or clear-cell tumors because those lesions have a higher incidence of nodal spread. For adequate nodal sampling, most of the lymph nodes from the external iliac, hypogastric, obturator, and lower common iliac vessels should be removed. Multi-site sampling, with evaluation of at least 10 pelvic lymph nodes, is adequate, and any additional information gained from a complete lymph adenectomy amounts to only a few percent.[35] Node sampling adds little time and negligible complications to the hysterectomy; it should be done liberally because retrospective evidence indicates that pelvic lymph node biopsy may improve the overall outcome for patients with endometrial cancer, especially those with grade 3 tumors.[36] Overall, the risk of para-aortic nodal metastasis is quite low, so node sampling may not be worthwhile in all patients with endometrial cancer. However, node sampling should be considered in those with more than a 5% risk of para-aortic nodal metastasis, those who in the Gynecologic Oncology Group (GOG) staging study were noted to have deeply invasive grade 3 tumors, cervical stromal involvement, positive pelvic nodes, and extrauterine disease.[34] In addition, sampling should be considered in all grade 3 papillaryserous or clear cell tumors, moderately invasive grade 2 tumors, and deeply invasive grade 1 tumors. Although lymph node size is not a definite indicator of metastatic disease, all enlarged lymph nodes should be removed.[37] A slightly increased mortality rate, mainly due to embolic complications, and an increased transfusion rate have been reported after pelvic and para-aortic lymph adenectomy,[38] but these increases have been disputed by others.[39]

UTERINE SARCOMA

The staging system developed for endometrial cancer is used for staging uterine sarcomas.

FALLOPIAN TUBE MALIGNANCIES

Adenocarcinomas of the fallopian tube are rarely diagnosed. In the advanced stage, it is impossible to differentiate them from adenocarcinomas of the ovary. Staging and diagnostic procedures are similar to those for ovarian cancer.[40]

OVARIAN CANCER

Symptoms

Ovarian cancer is the most feared gynecological malignancy because it has no early warning signs. Moderate enlargement of the ovary or even a pelvic mass often do not cause any symptoms. The signs of secondary organ involvement such as abdominal pain, decreased appetite, early satiety, and ascites typically prompt the patient to undergo evaluation. On pelvic exam, a firm, multinodular, fixated adnexal mass or a mass with nodularity in the cul-de-sac are pathognomonic. On abdominal exam, a large pelvic mass or an upper abdominal mass, such as an omental tumor, may sometimes be felt. The most characteristic sign is ascites. Careful examination of the lungs is important because pleural effusion is one of the most frequent signs of metastatic disease. Sometimes inguinal lymph nodes, and rarely supraclavicular lymph nodes, are enlarged.[41]

Diagnosis

A laboratory survey should be obtained. However, tumor markers are rarely useful in establishing the diagnosis. The CA-125 level is not reliably elevated in patients with early disease, but can be elevated in a variety of other benign or malignant conditions, especially in premenopausal women.[42] The carcino-embryonic antigen (CEA) level is not useful in distinguishing an ovarian tumor from a metastatic gastrointestinal tumor because it is elevated in about 30% of primary ovarian lesions.[43] Other tumor markers (AFP, HCG, LDH) are most useful in young patients in their second or third decade with an ovarian mass when germ cell tumors are more frequent.[44]

The best method for evaluating the ovary is an ultrasound exam[45] because it not only determines the size of the ovarian mass, but also reveals tumor characteristics such as septations, papillations, and solid areas. Several scoring systems have been developed and are quite accurate in assessing the risk of an ovarian malignancy, but they cannot replace the histological evaluation. A chest x-ray is necessary to check for pleural effusions. In patients who are candidates for surgery, a CT scan of the abdomen and pelvis rarely gives information which would change the treatment plan.[41] Patients should be current on screening exams such as mammography and colonoscopy. Any gastrointestinal symptoms, especially from the lower gastrointestinal tract, should be carefully evaluated to rule out another primary tumor which could have caused an ovarian metastasis.[46] In addition, the presence of advanced pelvic disease makes it difficult to fully evaluate the sigmoid colon at the time of surgery. If tumor involvement is known preoperatively, the patient can be prepared for bowel resection.

Staging

The staging of ovarian cancer is surgical and focuses on the presence of extraovarian disease.[1,2] At exploratory laparotomy, careful inspection of the entire abdominal cavity and collection of washings from the pelvis, both gutters, and the diaphragm, are the initial steps.[47] The ovaries are closely inspected in stage I disease. A macroscopic or microscopic tumor which has spread

"The best method for evaluating the ovary is an ultrasound exam because it not only determines the size of the ovarian mass, but also reveals tumor characteristics such as septations, papillations, and solid areas."

TABLE 4. STAGING OF OVARIAN CANCER

FIGO			TNM
Stage I		Growth limited to the ovary	T1
	Stage Ia	Growth limited to one ovary; no ascites No tumor on the external surface; capsule intact	T1a N0 M0
	Stage Ib	Growth limited to both ovaries; no ascites No tumor on the external surface; capsules intact	T1b N0 M0
	Stage Ic	Tumor either Stage Ia or Ib, but with tumor on surface of one or both ovaries; or with capsules ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings	T1c N0 M0
Stage II			T2
	Stage IIa	Extension or metastases to the uterus or tubes or both	T2a N0 M0
	Stage IIb	Extension to other pelvic tissues	T2b N0 M0
	Stage IIc	Tumor either Stage IIa or IIb, but with tumor on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings	T2c N0 M0
Stage III		Tumor involving one or both ovaries with peritoneal implants outside the pelvis, positive retroperitoneal or inguinal nodes, or both. Superficial liver metastasis equals Stage III	T3
	Stage IIIa	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces	T3a N0 M0
	Stage IIIb	Tumor involving one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces <2 cm in diameter. Nodes are negative	T3b N0 M0
	Stage IIIc	Abdominal implants >2 cm in diameter, positive retroperitoneal or inguinal nodes, or both	T3c N0 M0 T1–3 N1 M0
Stage IV		Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV	T4 T any N any M1

FIGO=Fédération Internationale de Gynécologie et d'Obstétrique.

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TABLE 5. STAGING OF GESTATIONAL TROPHOBLASTIC DISEASE

Prognostic Factor	Prognostic Score 0	1	2	4
Age (years)	<39	>39	—	—
Antecedent pregnancy	Hydatid mole	Abortion	Term	—
Interval between end of antecedent pregnancy and start of chemotherapy (months)	<4	4–6	7–12	>12
β-HCG (mIU/ml)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
ABO blood groups (female x male)	—	O x A	B	—
	—	A x O	AB	—
Largest tumor, including uterine (cm)	—	3–5	>5	—
Site of metastases	Lung, vagina, pelvis	Spleen, kidney	Gastrointestinal tract, liver	Brain
Number of metastases identified	—	1–4	5–8	>8
Prior chemotherapy	—	—	Single drug	Two or more drugs

Total score up to 4=low risk.
Total score 5 to 7=moderate risk.
Total score 8 or more=high risk.

β-HCG=human chorionic gonadotrophin (β=subunit).

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TABLE 6. GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

CLINICAL

I. Nonmetastatic GTD: No evidence of disease outside of uterus; not assigned to prognostic category.
II. Metastatic GTD: Any metastases
  A. Good-prognosis metastatic GTD
    1. Short duration (<4 months)
    2. Low β-HCG level (<40,000 mIU/ml serum)
    3. No metastases to brain or liver
    4. No antecedent term pregnancy
    5. No prior chemotherapy
  B. Poor-prognosis metastatic GTD: Any high-risk factor
    1. Long duration (>4 months since last pregnancy)
    2. High β-HCG level (>40,000 mIU/ml serum)
    3. Metastases to brain or liver
    4. Antecedent term pregnancy
    5. Prior chemotherapy

β-HCG=human chorionic gonodatrophin (β=subunit).

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to other organs in the pelvis is defined as stage II disease. Stage III encompasses peritoneal metastasis to the upper abdomen and nodal disease; tumor volume determines the substaging. Stage IIIA disease includes only microscopic metastatic implants in the upper abdomen. Stage IIIB disease has macroscopic implants <2 cm in diameter and stage IIIC disease is defined as tumor implants >2 cm in diameter. Any pelvic, para-aortic, or inguinal areas of nodal metastasis qualify as stage IIIC disease. Sampling of lymph nodes, including the pelvic and para-aortic nodes on both sides, is indicated for all patients who appear to have cancer that is stage IIIB or lower. Although complete lymph adenectomy has not been proven to improve outcome, bulky nodes should be removed to reduce tumor volume.[48] A definitive diagnosis of the type of ovarian tumor—epithelial, germ cell, abnormal, or other rare lesion—is made at time of surgery.[49]

GESTATIONAL TROPHOBLASTIC DISEASE

In the United States, gestational trophoblastic disease is quite rare. The diagnosis is most often made from a laboratory evaluation of a persistently elevated β-human chorionic gonadotrophin (HCG; β=subunit) titer in patients after molar pregnancy. Rarely, patients present with clinical symptoms such as irregular vaginal bleeding, spotting, or delayed postpartum hemorrhage. Very rarely, the initial sign is diffuse metastatic disease.[50] The staging is clinical because most patients will not undergo surgical treatment. A variety of staging systems are available. The original FIGO staging system for evaluating the anatomic spread of the disease within the pelvic or extrapelvic organs is rarely used.

A better predictor of prognosis is the clinical staging system or the World Health Organization staging system,[51] in which the main parameters are the β-HCG level, the areas of known metastatic disease, the number of tumors, and the size of the metastasis.

Initial evaluation of these patients starts with a pelvic ultrasound to rule out a normal pregnancy, then a chest x-ray. While a CT scan of the chest is more accurate in detecting pulmonary metastasis, its clinical importance is unclear.[52] Further work-up then includes a CT scan of the head to rule out brain metastasis, and a CT scan of the abdomen to rule out liver metastasis, both important factors in high-risk disease.[53] **OS**

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